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Thymosin α1 Enhances IL-15 Pathway Between MoDCs and CD8+ T Cells and Restrains HIV Latency In Vitro

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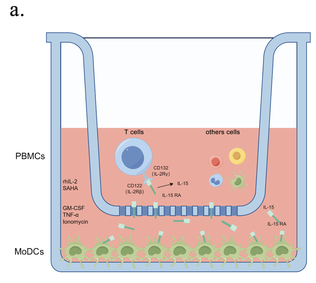
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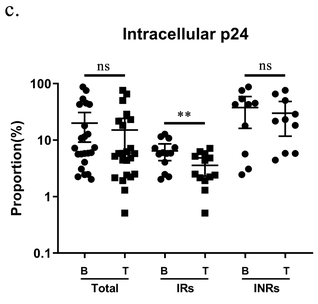
BACKGROUND

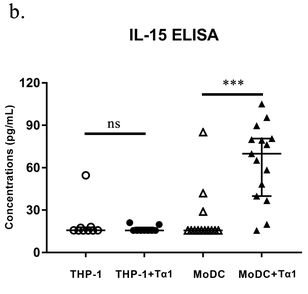
Viral reservoir presents a significant challenge in HIV-1 cure. Studies indicate that dendritic cells may limit HIV-1 reservoir by bolstering effector cell (including CD8+ T and NK cell) function via the IL-15 pathway and facilitating the expansion of virtual memory CD8+ T cells (T_{VM}). We previously observed that Thymosin α1 (Tα1) may restrict the reservoir through the IL-15 pathway, however, the precise mechanism remains to be fully elucidated.

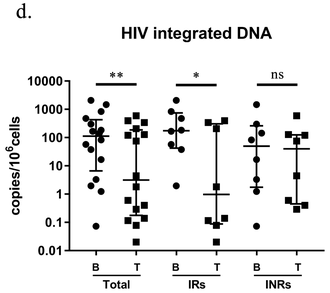
METHODS

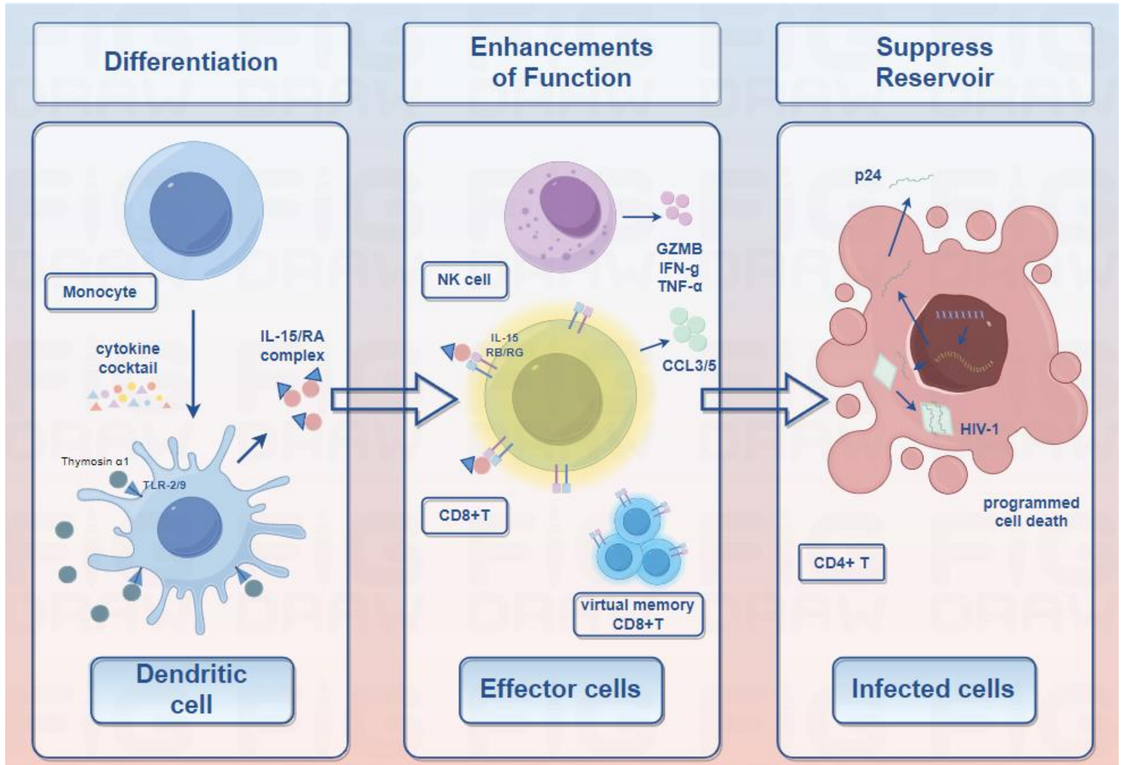
Peripheral blood mononuclear cells (PBMCs) were obtained from individuals living with HIV-1 (PLWH). In vitro, THP-1 cells were differentiated into mature monocyte-derived dendritic cells (MoDCs) and co-cultured with PBMCs under various conditions in a two-layer transwell model (Fig.a). To assess the levels of reservoir reactivation and effector cell functionality, flow cytometry was employed to measure changes in HIV-1 p24 protein levels in CD4+ T cells, cytokine/chemokine levels in effector cell, T_{VM} subpopulation proportions, and IL-2Rβ receptor expression on T_{VM} cells. Fluorescence quantitative PCR measured changes in HIV-1 integrated DNA levels to assess reservoir size.











·Thymosin α1 suppress HIV-1 reactivation and reservoir size in vitro.
·Thymosin α1 enhance effector cell function through IL-15 pathway between dendritic cells and effector cells.
·Thymosin α1 promote the proliferation of virtual memory CD8+ T cells.

RESULTS

In vitro, Tα1 stimulation of MoDCs resulted in significant secretion of IL-15/RA complexes (p<0.001, Fig.b). This interaction with IL-2Rβ/γ receptors on T cells inhibited p24 levels in CD4+ T cells (p=0.004, Fig.c), reduced HIV-1 integration DNA levels (p=0.012, Fig.d), and enhanced the intracellular secretion of CCL3/5, IFNγ, and TNFα in CD8+ T cells (p<0.05, Fig.e&f), IFNγ, TNFα and GZMB in NK cell (p<0.05, Fig.g), as well as proliferation of T_{VM} subpopulation (p=0.013, Fig.h) . The decreased degree of p24 level was negatively correlated with the secretion of intracellular cytokines in CD8+ T cells and the increase of T_{VM} proportions (p<0.05, Fig.i-k). However, these effects were observed in PBMCs from immunological responders (IRs) rather than nonresponders (INRs). Tα1 stimulation cannot alter the frequency of T_{VM} cells in INRs (p=0.126, Fig.l) and neither Tα1 nor rhIL-15 altered the expression of surface IL-2Rβ receptors (p>0.05, Fig.m), indicating impaired responsiveness of these subsets to IL-15 signaling.

CONCLUSIONS

This study demonstrate that Tα1 enhances effector cell function, promotes T_{VM} proliferation, and suppresses reservoir size and reactivation via IL-15 pathway activation in dendritic cells. Impaired IL-15 signaling responsiveness in INRs may contribute to poor reservoir control, highlighting a potential therapeutic target.

ADDITIONAL KEY INFORMATION

Ethics Statement

This study was approved by the Shanghai Public Health Clinical Center (SHPHCC) Ethics Committee (2020-S119-02, 2021-E021-02) in according to the guidelines of the Declaration of Helsinki. Written informed consent was obtained from all participants.

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